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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,663	09/23/2003	Victor C. Yang	30275/40871	5598

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@marshallip.com

Office Action Summary	Application No.	Applicant(s)	
	10/668,663	YANG ET AL.	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-50,55-68 and 70-75* is/are pending in the application.

4a) Of the above claim(s) *57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-50,55,56,59-68 and 70-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed on December 27, 2007 on March 27, 2008 and April 23, 2008 (Supplemental Response) have been received and entered.

Claim Disposition

2. Claims 48-50, 55-68 and 70-75 are pending (based the renumbering of the claims). Claims 48-50, 55-56 and 59-68 and 70-75 are under examination. Applicant is urged to renumber the claims as follows since two claims 70 was filed in the amendments filed on March 27, 2008 and April 23, 2008. Newly submitted claim 70 should be renumbered as claim 71; newly submitted claim 71 should be renumbered as claim 72; newly submitted claim 72 should be renumbered as claim 73; newly submitted claim73 should be renumbered as claim 74; and newly submitted claim 74 should be renumbered as claim 75.

Maintained-Specification Objection

3. The specification is objected to because of the following informalities:

As previously stated, the specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as TWEEN-20®, for example, have been noted in this application (see page 62). It should be

capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Correction of the above is required.

Maintained-Claim Objection

4. The claims are objected to because of the following informalities:

Claims 48-50 and 59-63 are objected to for improper dependency.

Claim 63 as amended is objected to for the recitation of "wherein at least a coagulant is further administered", for clarity, it is suggested that the claim is amended to read, "The method of claim 64, further comprising administering a coagulant to said mammal".

Correction is required.

Maintained and Amended-Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 48-50, 55-56, 59-68, 70-71 and 73-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method of inactivating heparin or low molecular weight heparin with purified protamine fragment. The claims are defined only by functional properties, not by a structure. Thus, there is no indication of which purified protamine fragment the claimed invention is directed to. Note for example that claim 67 is directed to a first and second protamine, which provides evidence that there can be more than one protamine fragments, however, no structure is provided. In addition the claims are directed to a method that utilizes the undefined protamine and a coagulant (see claim 63), which is also undefined. Furthermore, the art teaches that protamine given to neutralize heparin after extracorporeal circulation can trigger a catastrophic reaction in some patients (see Tan et al. Anesthesiology, Feb. 1989, vol. 70, no. 2, pages 267-75). Therefore, the claimed invention needs to adequately describe the protamine fragment intended in the method. Thus the claims lack adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed

invention. See *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997).* Therefore, a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. *See MPEP 2163.* The newly submitted claim also lack adequate written description because the claim does not set forth what effect of heparin is intended.

Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of encoded proteins, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of

isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993). See MPEP 2163.*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

6. Claims 71-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
The claims recite added material, which is not supported by the original disclosure. Claim 71 recites "proline-specific endoprotease" wherein the instant specification discloses "proline-specific endopeptidase" at paragraph [0053], for example and claim 72 recites "clupine protamine", whereas the instant specification discloses "clupeine protamine" at paragraph [003] for example. Therefore, the specification lacks adequate written description as no support was found in the instant specification for the above limitations in claims 71-72.

Response to Arguments

7. The responses filed have been considered, however, are not fully persuasive. As the amendment filed did not address the objection to the specification and claims the

objections remain. The rejection under 35 U.S.C. 112 first paragraph has been maintained, however is amended to add the newly submitted claims. Note also that a new ground of rejection is instituted under 35 U.S.C. 112, first paragraph written description pertaining to new matter for the reasons stated above.

Regarding the maintained rejection under 35 U.S.C. 112, first paragraph, the claims recite a protamine fragment that has reduced immunoresponsiveness or toxicity compared to native protamine. Applicant argues (see for example page 5 of the supplemental response) "...that the fact that full-length protamine is known in the art and its amino acid sequence understood..., it must be concluded that the specification expressly contemplates methods of inactivating heparin with protamine fragments having low level immunogenicity ...". The issue at hand is that what fragment is going to maintain the activity of the native. No structural limitations are provided in the claim as to what said fragment looks like.

The claimed protamine is modified to achieve the reduced immunoresponsiveness or toxicity, however, the claims do not establish what those modifications are. It is noted that the specification at paragraph [0109] discloses that ficin a plant protease cleaves protamine at the C-end and results in lower toxicity, however, the limitations of the specification cannot be read into the claims. Therefore, a skilled artisan would not be able to envision the detail chemical structure of the genus of protamine fragments encompassed in the claims. The art recognizes that the protamine structure comprises 31 amino acids per molecule and only five types of residues: arginine (20), glycine (6), serine (3), alanine (1) and tyrosine (1). The primary structure

of protamine is reported and the N-terminal sequence contains the four hydroxylated amino acids of the molecule; the C-terminal region shows a sequence of eleven adjacent residues of arginine and contains all the glycine residues present in the protein. However, there is no indicia as to where in the native structure modifications will occur such that the resultant effect is a fragment of protamine that has reduced immunoresponsiveness or toxicity and will inactive heparin or LMW heparin. Thus, the claims encompass a genus of fragments not adequately described.

It is noted that applicant argues that the structure is well established, however, the fragments are claimed and they are not adequately described. It is noted that newly submitted claims 71-72 addresses enzymatic cleavage of the protamine which would give a skilled artisan a glimpse of what the structure would look like based on the enzymes used, for example thermolysin which cuts at the N-terminal or ficin which cuts at the C-terminal. However, this limitation is not recited in the independent claim.. Applicant is urged to be explicit in which protease is used since the specification discloses at paragraph 0108 and 0109 the disadvantages/advantages (specifically thermolysin is not preferred) of each and indicates that ficin is preferred. For example, claim 55 recites "at least a purified protamine fragment effective to inactivate heparin or low molecular weight heparin; wherein said purified protamine fragment is bioactive, has a molecular weight of between about 400 and about 2500 Daltons as determined by gel filtration and has reduced immunoresponsiveness or toxicity compared to native protamine", however, no correlation is made between function and structure. As stated

about a skilled artisan cannot envision the detailed chemical structure of the claimed genus of protamine fragments. Thus, the rejection remains.

Conclusion

8. No claims are presently allowable.

9. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652